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10/588,334

08/03/2006

Craig Johnstone

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EXAMINER

ZAREK, PAUL E

ART UNIT

PAPER NUMBER

1617

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/588,334	<b>Applicant(s)</b> JOHNSTONE ET AL.	
	<b>Examiner</b> Paul Zarek	<b>Art Unit</b> 1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 05 December 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 18-35 is/are pending in the application.
- 4a) Of the above claim(s) 18-21, 26-29 and 33-35 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 22-25 and 30-32 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>08/03/2006, 09/10/2007, 11/20/2007, 09/24/2008</u> .          | 6) <input type="checkbox"/> Other: _____                          |



## **DETAILED ACTION**

### ***Status of the Claims***

1. Claims 18-35 are currently pending. This is the first Office Action on the merits of the claim(s).

### ***Election/Restrictions***

2. Applicants' election with traverse of Group III and the species of Example 3b in the reply filed on 12/05/2008 is acknowledged. The traversal is on the ground(s) that the art applied to break unity of invention did not anticipate or render obvious the claimed invention. Specifically, Boyd, et al., does not teach a phenoxy substituent linked to the central phenyl ring. Therefore, the applied art does not break unity of invention. This is not found persuasive. Applicants compare an embodiment of formula (I) to Example II107 disclosed in Boyd, et al. Applicants state that the tested compound and Example II107 "have broadly similar EC<sub>50</sub> values" (instant specification, pg 125, line 16) indicating the differences between the two molecules does not materially affect their abilities to activate glucokinase. One of ordinary skill would reasonably conclude that the substituent important for activating glucokinase is HET-1, and that the differences of a phenoxy vs. benzyloxy, or methoxymethyl vs. 1-methylethyl (instant application vs. Boyd, et al.) are inconsequential. Thus, the instant invention lacks inventive step, and therefore, a special technical feature linking the inventions

The requirement is still deemed proper and is therefore made FINAL.

Art Unit: 1617

3. During the course of the examination of the application, Examiner has found that a restriction between the various compound groups was improper. The restriction between the compounds (Groups I-V) is vacated. Claims 1-32 read on the elected Group. Claims 22-25 and 30-32 read on the elected species. Claims 1-21 and 26-29 are withdrawn as being drawn to a non-elected species. Claims 33-35 are withdrawn as being drawn to a nonelected group.

***Priority***

4. Applicant's claim for the benefit of a prior-filed international application PCT/GB05/00545 (filed on 02/12/2005) under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows: Applicant has not properly claimed the benefit of the prior-filed international application. To gain the benefit of a prior filed application, "[t]he later-filed application must contain a reference to the prior-filed application in the first sentence(s) of the specification or in an application data sheet, for a benefit claim under 35 U.S.C. 120, 121, or 365(c), and also for a benefit claim under 35 U.S.C. 119(e)." (MPEP 201.11(C)). The effective filing date of the instant application is 08/03/2006.

5. Acknowledgment is made of applicant's claim for foreign priority to United Kingdom applications 0403593.7, 04133863.4, and 04230379.7 (filed on 02/18/2004, 06/16/2004, and 10/16/2004, respectively) under 35 U.S.C. 119(a)-(d). The United Kingdom applications were filed more than a year prior to the filing of the instant application, and, hence, Applicant cannot claim priority to said document. There is currently no foreign priority of the instant application.

Art Unit: 1617

Applicant may gain the foreign priority by perfecting the claim for the benefit of the prior-filed international application PCT/GB05/00545.

### ***Information Disclosure Statement***

6. The references cited by applicants in the information disclosure statement filed March 1, 2007 have been made of record. The Examiner has considered the voluminous references to the best of his ability.

While the statement filed does not comply with the guidelines set forth in MPEP 2004 regarding both the number of references cited and the elimination of clearly irrelevant art and marginally cumulative information, compliance with these guidelines is not mandatory. Furthermore, 37 CFR 1.97 and 1.98 does not require that the information be material; rather, they allow for submission of information regardless of its pertinence to the claimed invention. Also, there is no requirement to explain the materiality of the submitted references. However, the cloaking of a clearly relevant reference by inclusion in a long list of citations may not comply with the Applicant's duty of disclosure. *Penn Yan Boats, Inc. v. Sea Lark Boats Inc.* 359 F. Supp. 948, (S.D. Fla. 1972).

Applicant is advised that the MPEP states the following with respect to large information disclosure statements:

Although a concise explanation of the relevance of the information is not required for English language information, applicants are encouraged to provide a concise explanation of why the English-language information is being submitted and how it is understood to be relevant. Concise explanations (especially those which point out the relevant pages and lines) are helpful to the Office, particularly where documents are lengthy and complex and applicant is aware of a section that is highly relevant to patentability or where a large number of documents are submitted and applicant is aware that one or more are highly relevant to patentability. MPEP § 609.04(a)(III).

Art Unit: 1617

This statement is in accord with dicta from *Molins PLC v. Textron, Inc.*, 48 F.3d 1172 (Fed. Cir. 1995), stating that forcing the Examiner to find “a needle in a haystack” is “probative of bath faith.” *Id.* at 1888. This case presented a situation where the disclosure was in excess of 700 pages and contained more than fifty references. *Id.*

### ***Claim Objections***

7. Claims 22, 23, and 30-32 are objected to because of the following informalities: The limitation in Claim 22 for R<sup>4</sup> lists HET-2 twice. Claim 23 depends upon Claim 22 and contains all the limitations therein. Claims 30-32 refer to the compounds of Claim 22 and contain all the limitations of the compounds therein. Appropriate correction is required.

### ***Claim Rejections - 35 USC § 112 (1<sup>st</sup> paragraph)***

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 22-25 and 30-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the compounds of formula (I), and salts thereof, methods of treating a disease with said compounds and salts, and a method of making said compound and salts, does not reasonably provide enablement for the prodrug or solvate of formula (I), or methods of making or using said prodrugs or solvates. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Art Unit: 1617

10. *In re Wands*, 858 F.2d at 736-40, 8 USPQ2d at 1403-07, set forth eight factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is “undue.” (MPEP § 2164.01(a))

- a. *The breadth of the claim*: Claims 18-32 are drawn to compounds or pharmaceutical compositions of formula (I), and salts, prodrugs and solvates, thereof. The instant specification defines pro-drug to be a bioprecursor or pharmaceutically acceptable compound being degradable in the body to produce the compound of the invention (pg 55, lines 27-30);
- b. *Nature of the invention*: The nature of the invention is a compound of formula (I), or a salt thereof, and its method of use to treat a GLK mediated disorder, and a method of making formula (I) or a salt thereof.;
- c. *The state of the prior art*: Prodrugs are known in the art and are utilized to improve the targeting or pharmacokinetics of a given drug. Van de Waterbeemd, et al. (Journal of Medicinal Chemistry, 2001), teach the myriad considerations one must keep in mind when designing prodrugs (pgs 1314-1327).

Approximately one third of drugs are capable of forming crystalline hydrates (Vippagunta, et al., Advanced Drug Delivery Reviews, 2001, pg 15, section 3.1).

Byrn, et al. (Solid State Chemistry of Drugs, 1999), teach that “[t]he occurrence of hydrated or solvated crystal forms, crystals in which solvent molecules occupy regular positions in the crystal structure, is widespread but by no means universal among drug



Art Unit: 1617

substances." (pg 232, emphasis added). Most drug crystals that fall into the category of solvates are hydrates (pg 236).

Byrn, et al., note that the water molecule is particularly suited to fill structural voids, due to its small size. In hydrated crystal structures, water molecules bind to other water molecules but also to any available functional group, i.e. carbonyls, amines, alcohols, and many others which are capable of accepting or donating an active hydrogen atom to form hydrogen bonds (pg 236, "Hydrates"). The behavior of hydrates of pharmaceuticals is unpredictable due to dehydration prior to melting, and cracking during dehydration (pg 234). Also hydrates and solvates may only be formed under certain conditions, dependent upon the compounds sought to be crystallized. Such a process is not a given in pharmacology and requires a great deal of research, with no reasonable expectation of success.

Furthermore, the stability of solvates and hydrates is not altogether predictable, wherein said stability directly affects the properties of a given molecule. This lack of stability means a hydrate or solvate, if found to possess similar properties as the target compound, may not function as intended, *in vivo*. Such facts lead to the conclusion that more than a mere recitation is needed in order to support a claim to solvates and hydrates. Creating functional solvates and hydrates with the same properties as the mother-compound is by no means routine, thus there must be a showing sufficient to satisfy the enablement requirement;

Art Unit: 1617

- d. *Level of one of ordinary skill in the art:* One of ordinary skill in the art would comprise medicinal chemists and scientists and physicians investigating glucose metabolism and/or diabetes. The level of skill would be high;
- e. *Level of predictability in the art:* Numerous factors must be considered when attempting to create a prodrug. Van de Waterbeemd, et al., state that even with high-throughput screening and combinatorial chemistry, "the attrition of the eventual development candidates is still very high mainly due to toxicity and/or poor [pharmacokinetic] properties" (pg 1327, "Future Directions" paragraph 1, emphasis added). It cannot be known *a priori* whether a given molecule will be an effective prodrug. High-throughput computer modeling is not yet competent to reliably predict whether a given molecule would be an effective prodrug of a given drug. As such, "there remains a need for relatively low-throughput animal studies to extrapolate the likely clinical pharmacokinetic profile (van de Waterbeemd, et al., pg 1328, paragraph 1). Van de Waterbeemd, et al., further teach that it is unclear which mathematical models would be most suited to predict pharmacokinetic properties of a given molecule in lieu of experimental data (pg 1328, paragraph 3). Finally, van de Waterbeemd, et al., discuss that "much needs to be learned about transporters influencing either active drug uptake or efflux of orally administered drugs. In addition, it will be important to develop screens to assess its extent" (pg 1328, "Conclusions).

Just because many drugs are capable of forming hydrates or solvates does not mean that the resulting hydrate or solvate can be predicted before hand. Vippagunta, et al., teach that predicting the formation of solvates or hydrates of a compound is "complex

Art Unit: 1617

and difficult." "There may be too many possibilities so that no computer programs are currently available for predicting the crystal structures of hydrates and solvates." pg 18, Section 3.4). Byrn, et al., disclose that the properties of solvates and hydrates of a given drug can only be determined empirically;

f. *Amount of direction provided by the inventor:* Applicants contemplate prodrugs and solvates and cite art generically teaching how a skilled artisan would generate a prodrug. There is no substantive discussion of solvate in the instant specification;

g. *Existence of working examples:* Applicants provide numerous examples of compounds of formula (I), but no prodrugs or solvates, thereof; and,

h. *Quantity or experimentation needed to make or use the invention based on the content of the disclosure:* Predicting if a certain molecule is in fact a prodrug that produces the active compound metabolically, *in vivo*, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental science. For a compound to be a prodrug, it must meet three tests: A) it must itself be biologically inactive; B) it must be metabolized to a second substance, *in vivo*, at a rate and to an extent to produce that second substance at a physiologically meaningful concentration; and C) the second substance must be clinically effective. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation. The instant specification does not provide enabling guidance sufficient that one of ordinary skill in the art would understand which of the

Art Unit: 1617

potentially limitless candidates would be a legitimate prodrug of the formula (I). The prior art does not compensate for this deficiency.

Byrn, et al., and Vippagunta, et al., are explicit in their statements that the formation of solvates or hydrates can not be known without experimentation. Indeed, one of ordinary skill in the art could not ascertain which solvates or hydrates would form with any reasonable expectation of success. The instant specification does not make up for this deficiency, as there is no guidance to an ordinarily skilled artisan to either make a solvate or hydrate of formula (I). Undue and unpredictable experimentation would be required to use the invention as claimed. Therefore, the instant specification and prior art would not enable one of ordinary skill in the art at the time the invention was made to make and use the invention commensurate with the scope of the rejected claims.

11. Claims 22, 23, and 30-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for R<sup>6</sup> to be a substituted or unsubstituted C<sub>1</sub>-C<sub>4</sub> alkyl, does not reasonably provide enablement for R<sup>6</sup> to be HET-4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The Wands factors are addressed below:

a. *The breadth of the claim:* The rejected claims are drawn to a compound of formula (I) or method of making or using said compounds. The compounds contain the subgroup HET-1 which is optionally substituted by R<sup>6</sup>. R<sup>6</sup> can be a substituted or unsubstituted C<sub>1</sub>-C<sub>4</sub> alkyl or a 5-6 membered heteroaryl ring containing 1, 2, or 3 heteroatoms. Heteroatoms can be nitrogen, oxygen, and sulfur;

Art Unit: 1617

- b. *Nature of the invention*: see above;
- c. *The state of the prior art*: Compounds similar to but not obvious over those of the instant application are disclosed in the prior art as glucokinase activating agents. For example, Boyd, et al. (International Application No. WO 03/015774, already of record), disclose an exceedingly vast number of compounds that generally differ from those of the instant application in that Boyd, et al., teach a benzyloxy substituent linked to the central phenyl ring, whereas the compounds of the instant application are possess a phenoxy substituent linked to the central phenyl ring. Of the large number of compounds disclosed, only 3 contain rings on HET-1 (II-121, II-153, and JJ-42) ;
- d. *Level of one of ordinary skill in the art*: see above;
- e. *Level of predictability in the art*: The pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher* (427 F. 2d 833, 166USPQ 18 (CCPA 1970)) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. The level of unpredictability in this art is very high;
- f. *Amount of direction provided by the inventor*: Applicants do not discuss the role of the HET-1 substituent and its effect on binding to or activating glucokinase;
- g. *Existence of working examples*: There are no working examples or disclosed embodiments in which R<sup>6</sup> is HET-4. Moreover, Applicants have demonstrated the effect of only a single compound (Example 11b) on serum glucose levels (“Biological Tests”); and,

Art Unit: 1617

h. *Quantity or experimentation needed to make or use the invention based on the content of the disclosure:* Applicant has made and tested only a very small subset of the possible compounds encompassed by the rejected claims. The instant specification does not provide sufficient guidance to enable one of ordinary skill in the art at the time the invention was made to make all of the huge number of compounds claimed. “Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. . . . [M]ost syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence” (Dorwald, *Side Reactions in Organic Synthesis*, 2005).

Moreover, Applicant has not provided any data suggesting that any molecule other than the small, disclosed subset of compounds would be effective glucokinase activating agents. The possible embodiments claimed are not necessarily obvious variants of each other. “A patent is not a hunting license. It is not a reward for search but compensation for its successful conclusion and patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable.” (*Genentech Inc v Nova Nordisk* 42 USPQ 2d 1001) One of ordinary skill could not reasonably determine whether the claimed compounds would be glucokinase activating agents. The instant specification does not enable one of

Art Unit: 1617

ordinary skill in the art to make and use the invention commensurate with the scope of the rejected claims. Undue and unpredictable experimentation would be required.

12. Claims 22 and 30-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for HET-2 and HET-3 being a C<sub>4</sub>-C<sub>6</sub> cycloalkyl or heterocycloalkyl substituted with up to 2 heteroatoms of nitrogen, oxygen, and sulfur, does not reasonably provide enablement for HET-2 and HET-3 comprising other substituents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The Wands Factors are addressed below:

- a. *The breadth of the claim:* The rejected claims limit HET-2 and HET-3 to be a wide variety of compounds. HET-2 can be from 4-6 atoms, with up to 4 carbons replaced by heteroatoms. Moreover, an additional -CH<sub>2</sub>- group can be replaced with a -C(O)- or oxidized sulfur (i.e. -S(O)- or -S(O)<sub>2</sub>-). HET-3 can be a 4-7 membered saturated or unsaturated ring comprising up to 2 heteroatoms and an additional -C(O)- or oxidized sulfur to replace a -CH<sub>2</sub>-. HET-3 may also be a 6-10 membered bicyclic ring system containing up to 2 heteroatoms;
- b. *The state of the prior art:* see above;
- c. *Level of one of ordinary skill in the art:* see above;
- d. *Level of predictability in the art:* The pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher* (427 F. 2d 833, 166USPQ 18 (CCPA 1970)) indicates that the more unpredictable

Art Unit: 1617

an area is, the more specific enablement is necessary in order to satisfy the statute. The level of unpredictability in this art is very high;

e. *Amount of direction provided by the inventor:* Applicants do not discuss the role of the HET-2 or HET-3 substituents and their effect on binding to or activating glucokinase;

f. *Existence of working examples:* There are no working examples or disclosed embodiments in which HET-2 or HET-3 are outside the scope of the rejected claims. Moreover, Applicants have demonstrated the effect of only a single compound (Example 11b) on serum glucose levels (“Biological Tests”). The tested compound does not contain HET-2 or HET-3; and,

g. *Quantity or experimentation needed to make or use the invention based on the content of the disclosure:* Applicant has made and tested only a very small subset of the possible compounds encompassed by the rejected claims. The instant specification does not provide sufficient guidance to enable one of ordinary skill in the art at the time the invention was made to make all of the huge number of compounds claimed. “Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. . . . [M]ost syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence” (Dorwald, Side Reactions in Organic Synthesis, 2005).



Art Unit: 1617

Moreover, Applicant has not provided any data suggesting that any molecule other than the small, disclosed subset of compounds would be effective glucokinase activating agents. The possible embodiments claimed are not necessarily obvious variants of each other. "A patent is not a hunting license. It is not a reward for search but compensation for its successful conclusion and patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable." (*Genentech Inc v Nova Nordisk* 42 USPQ 2d 1001) One of ordinary skill could not reasonably determine whether the claimed compounds would be glucokinase activating agents. The instant specification does not enable one of ordinary skill in the art to make and use the invention commensurate with the scope of the rejected claims. Undue and unpredictable experimentation would be required.

***Claim Rejections - 35 USC § 112 (2<sup>nd</sup> paragraph)***

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 22 and 30-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 22 contains the limitation that HET-2 may be optionally substituted by R<sup>7</sup>. R<sup>7</sup> may be -C(O)NR<sup>4</sup>R<sup>5</sup>. R<sup>4</sup> may be HET-2. HET-2, then, may be optionally substituted by R<sup>7</sup>. The claim does not contain any limitation as to the number of times that this cycle can be repeated such that the claim is rendered indefinite. Claims 30-32 depend upon Claim 2, contain all the limitations thereof, and are therefore also rejected as indefinite.

Art Unit: 1617

15. Claims 22 and 30-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 22 recites the limitations defining R<sup>4</sup>, R<sup>5</sup>, R<sup>7</sup>, and HET-2. None of formula (I), R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>6</sup>, R<sup>8</sup>, HET-1, HET-3, or HET-4 list R<sup>4</sup>, R<sup>5</sup>, R<sup>7</sup>, and HET-2 as a possible substituent. There is insufficient antecedent basis for this limitation in the claim.

16. Claims 22 and 30-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 22 recites the limitation of HET-2 or R<sup>4</sup> “optionally substituted” with R<sup>7</sup>, or the limitation HET-3 “optionally substituted” by R<sup>8</sup> or R<sup>3</sup>. “Optionally substituted” is not defined in the instant specification and it is unclear the degree of substitution that would be allowed by the rejected claim. Thus, Claim 22 is indefinite. Claims 30-32 depend upon Claim 2, contain all the limitations thereof, and are therefore also rejected as indefinite.

### ***Claim Rejections - 35 USC § 103***

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

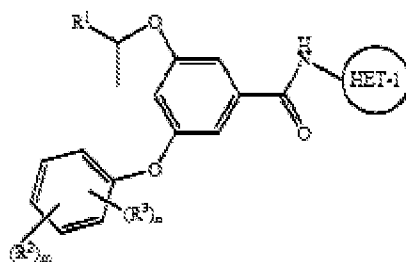
18. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

Art Unit: 1617

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

19. Claims 22-25 and 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boyd, et al. (International Application No. WO 03/015774, provided in IDS).

20. Claim 22 is drawn to a compound of Formula (I) containing the following core:



Claim 23 limits HET-3 of Formula (I) to a 4-6 membered ring. Claims 24 and 25 limit formula (I) to specific compounds. Claim 30 limits Formula (I) such that the R<sup>1</sup> is in the (S) configuration. Claim 31 limits the compound of Formula (I) wherein HET-1 is a 5-membered ring. Claim 32 is drawn to a pharmaceutical composition comprising a compound of Formula I. The elected species 3-(4-(azetidine-1-carbonyl)phenoxy)-5-[(1S)-methoxy-(1-methylethyl)oxy]-N-(1-methyl-1H-pyrazol-3-yl)benzamide (Example 3b) reads on Claims 22-25 and 30-32.

21. Boyd, et al., teach numerous glucokinase activating agents (abstract), and pharmaceutical compositions thereof (pg 1, line 8) with a structure similar but not identical to instantly claimed Formula (I). The compounds of Boyd, et al., contain the following generic formula:

Art Unit: 1617



wherein R3 can be either a pyrazole (Table GG, pg 90) or thiazole (Table II, pg 96). Examples GG2-4, 6, and 7 disclose a 1-methyl group on the pyrazole. Examples II100, 107, and 108 teach a 1-methyl group on the thiazole. Boyd, et al., teach a benzyloxy substituent linked to the central phenyl ring, whereas the instant application is drawn to a phenoxy substituent linked to the central phenyl ring. Furthermore, Boyd, et al., do not teach a (1S)-methoxy-(1-methylethyl)oxy group as R<sup>3</sup>.

22. Applicants admit in the instant specification that the instantly disclosed compound, Example 11b (which is not the elected species), and II107 of Boyd, et al., “have broadly similar EC<sub>50</sub> values” (pg 125, line 16). By this statement, one of ordinary skill in the art at the time the invention was made would reasonably conclude that the genus of compounds of the instant application would be glucokinase activating agents, just like those compounds disclosed by Boyd, et al. Therefore, in the absence of unexpected results, the instant invention and elected species are *prima facie* obvious over those taught by Boyd, et al.

23. Applicants further disclose that the compounds of the instant invention are “a selected subgroup of those described in [Boyd, et al.]” which possess “more advantageous physical properties” (pg 3, lines 27-30). Examiner interprets the disclosed physical properties to indicate enhanced bioavailability. Applicants’ disclosure of a single compound (Example 11b) possessing enhanced bioavailable is not sufficient to generally state that all or a significant portion of the claimed invention would also have unexpectedly higher bioavailability. “Whether

Art Unit: 1617

the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the ‘objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support.’ In other words, the showing of unexpected results must be reviewed to see if the results occur over the entire claimed range. *In re Clemens*, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980)” (MPEP § 716.02 (d)). In the present instance, Applicants have not demonstrated unexpectedly enhanced bioavailability of a sufficient number of compounds commensurate with the scope of the claims.

### ***Double Patenting***

24. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

25. Claims 22, 23, and 30-32 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 19-22, and 30 of copending

Art Unit: 1617

Application No. 11/665,222. Claims 22, 23, and 30-32 of the instant application correspond to Claims 19, 22, 20, 21, and 30 of the copending '222 application. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds differ only in the substituent of R<sup>1</sup>. The instant application, R<sup>1</sup> is methoxymethyl, whereas in the '222 application, R<sup>1</sup> is hydroxymethyl. The instant specification compares an Example 11b to II107 of Boyd, et al., and concludes that both have comparable activities in activating glucokinase. That II107 taught by Boyd, et al., lacks both a methoxymethyl or hydroxymethyl at R<sup>1</sup> indicates that neither are crucial for activating glucokinase. Therefore, the compounds of the instant application and the '222 application are obvious variants over each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

26. Claims 22, 23, and 30-32 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 19-22 and 30 of copending Application No. 11/665,163. Claims 22, 23, and 30-32 of the instant application correspond to Claims 19, 22, 20, 21, and 30 of the copending '163 application. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds differ only in the substituent at the 5 position of the central phenyl ring. In the instant application, the substituent is 2-methoxy-1-methylethoxy, whereas in the copending '163 application, the substituent is 3-methoxy-1-methylpropoxy. Homologs are *prima facie* obvious over each other (MPEP § 2144.09(II)).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***Conclusion***

27. Claims 22-25 and 30-32 are rejected.

28. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul Zarek whose telephone number is (571) 270-5754. The examiner can normally be reached on Monday-Thursday, 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

PEZ

/Rita J. Desai/  
Primary Examiner, Art Unit 1625